Blastomycosis: a new endemic focus in Canada

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A survey of the 38 patients resident in Ontario from whose sputum, body fluids or tissues *Blastomyces dermatitidis* was cultured by our laboratory between 1970 and 1981 revealed a new endemic focus to the north and east of Lake Superior, where 20 of 27 traceable patients lived. Direct microscopy revealed *B. dermatitidis* in 90% of the cases. A lack of clinical awareness, however, had often resulted in a delay (average 15 weeks) in diagnosis. In two cases the disease was identified only at autopsy. About 80% of the patients survived.

Les cultures des crachats et des liquides ou tissus corporels effectuées dans notre laboratoire entre 1970 et 1981 ont permis d'identifier du *Blastomyces dermatitidis* chez 38 patients habitant l'Ontario. Une enquête réalisée chez ces patients a mis en évidence un nouveau foyer endémique situé au nord et à l'est du lac Supérieur, où 20 des 27 patients qui purent être retracés vivaient. La microscopie directe révélait du *B. dermatitidis* dans 90% des cas. Plusieurs fois, cependant, un manque d'intuition clinique avait entraîné un délai de diagnostic (de 15 semaines en moyenne). Dans deux cas la maladie ne fut identifiée qu'à l'autopsie. Environ 80% des patients ont servécu.

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Blastomycosis, a fungal infection that can mimic several other diseases, is caused by the dimorphic fungus *Blastomyces dermatitidis*. The organism has rarely been isolated from the natural environment.[1,2] It may live in soils enriched by bird droppings, but soil streptomycetes can lyse *B. dermatitidis*;[3,4] this may account for the low rate of isolation from soil. Perhaps the fungus grows in the mycelial (saprophytic) form only under particular conditions of temperature and humidity, producing then the conidia that are infective. When the fungus is disturbed, hyphal fragments and conidia become airborne and could be inhaled by humans.[5] The parasitic form, a yeast, would then develop. Alternatively, it is possible that specific nutrients can bring about conversion to the yeast form, which could be inhaled directly.[6]

The disease has been reported world-wide.[1] The endemic areas in North America include Mexico, the southeastern United States, the Mississippi valley, the upper midwestern states and some parts of Canada.[7,8] In Canada 51% of the cases reported have occurred in Quebec, 23% in Ontario and 25% in Manitoba.[9] Because Sioux Lookout, in northern Ontario, is an endemic area for blastomycosis, cases are documented regularly, albeit rarely.

We report the results of a clinical and epidemiologic survey and discuss the value of simple light microscopy in making a prompt diagnosis.

Material and methods

Between January 1970 and December 1981 inclusive the medical mycology laboratory had identified *B. dermatitidis* by culturing sputum, body fluid and tissue samples[10,11] from 38 patients. The specimens had been sent to the laboratory for a diagnosis. Clinical information was obtained for 28 of the patients by sending a questionnaire to the physicians or through personal communication with the physicians.

The specimens were examined in a mount of 25% sodium hydroxide and 5% glycerol by direct microscopy. Isolation and identification was achieved with the following primary media: peptone dextrose agar with chloramphenicol, cycloheximide and gentamicin (CCG); blood agar with CCG; blood agar with CCG and 3% egg white; and Littman agar. The addition of egg albumin[12,13] prevented overgrowth of the blood agar by *Candida albicans*, which is often present in sputum.

The only condition known to be necessary for the conversion of *B. dermatitidis* to the yeast form is a temperature of 37°C. A chemically defined conversion medium introduced by one of the authors (J.K.) permitted more rapid conversion at 37°C,[6] leading to microscopic confirmation of the isolates' identity within 24 to 72 hours. At 26°C the complete medium stimulated the conversion of the mould to the yeast form. This conversion was nutrition- rather than temperature-dependent.

Results

Patients

There were 24 males and 4 females among the patients whose physicians responded to our questions, but we could not obtain all the information sought in every case.

The ages of 27 of the patients ranged from 2 to 75 years, with a mean of 44.2 years. Three were under the age of 16 years. Of the 27 patients for whom residence was recorded (Table I), 20 (74%) lived in small resource-based towns in northern Ontario, 4 lived in Toronto and 1 each lived in Oshawa, Hamilton and Sudbury. Detailed travel histories were not available for the patients who lived outside northern Ontario, but one who had lived in Toronto and another in Hamilton had been to Florida. Nine (43%) of the 21 adults for whom an occupational history was available had engaged in some form of outdoor work or activity. Five (23%) of the 21 had worked with wood (1 as a papermill worker, 2 as carpenters and 2 as lumber workers).

Overall, 23 (82%) of the 28 patients had pulmonary disease. It was the sole manifestation of blastomycosis in 11 (39%) of the 28. Of the 28 patients 8 (28%) had osseous involvement, 6 (21%) had cutaneous disease and 2 (7%) had central nervous system involvement; in 2 patients, only cutaneous lesions were present.

Table I—Places of residence of 27 patients with blastomycosis in Ontario

Town or city	No. of cases
Atikokan	1
Barrie	1
Chapleau	2
Espanola	3
Fort Frances	2
Gault	1
Georgetown	1
Hamilton	1
Hornepayne	1
Iroquois Falls	1
Mattawa	1
Northern Ontario (town unknown)	1
Oshawa	1
Smooth Rock Falls	1
Stouffville	1
Sudbury	1
Sundridge	1
Toronto	4
Valcaron	1
West Gilford (Haliburton)	1

Of the 26 patients for whom information on associated diseases and chemotherapy was recorded, 6 (23%) had an immunocompromising illness or were receiving a drug that was immunosuppressive, or both. One of these patients had sarcoidosis, one had glomerulonephritis that was being treated with steroids, one had lung cancer and was being treated with cyclophosphamide, vincristine and irradiation, one had diabetes mellitus and two were heavy consumers of alcohol. The other 20 patients were well, apart from having blastomycosis.

In five patients blastomycosis was diagnosed within 1 or 2 weeks, in three a year elapsed between the initial assessment and the diagnosis, and in two the diagnosis was made only at autopsy. The mean time to diagnosis was 14.9 weeks.

Five (18%) of the 28 patients died, all from the blastomycosis. Two were immunosuppressed (they had glomerulonephritis and carcinoma of the lung), one had a brain abscess, one had extensive pneumonia and one had disseminated blastomycosis diagnosed late in the course of the disease.

Mycologic findings

In specimens from 90% of the patients direct microscopy of a sodium hydroxide mount revealed the characteristic yeast cells. Blastomycosis was confirmed in all patients by isolation of the organism. *B. dermatitidis* was isolated from sputum samples on blood agar with CCG and 3% egg white; peptone dextrose agar and Littman's agar were the least useful. It was isolated from body fluids and tissue on peptone dextrose agar and on blood agar with CCG.

Discussion

The mean age in our series (about 45 years) is in accord with the results of other surveys.[7,14,15] The apparent association of the disease with outdoor occupations may partly account for the much greater number of cases in men. There seemed to be a lesser association between infection and occupational or recreational exposure to wood. Epidemics of blastomycosis have been reported in relation to the building of a hunting lodge,[16] construction sites[17] and other types of exposure to wood.[5] All the towns in which blastomycosis was found had a lumber industry — but so do many other towns in which blastomycosis has not been reported. Sioux Lookout and the areas north and east of Lake Superior appear to be endemic regions.

That pulmonary involvement, with respiratory symptoms, was the most common manifestation of blastomycosis in this series is in agreement with the results of other investigations.[14] A diagnosis is seldom made at this stage because of the nonspecific clinical and radiologic findings; the pneumonia may even improve while dissemination is occurring.[18]

Most of the patients in our series appeared not to have other illnesses or to be receiving drugs that could have compromised their immunologic systems, a finding consistent with other published data.[19] Most of them survived, again paralleling the observations of other authors.[20] On average, though, nearly 15 weeks passed between the first assessment by a physician and the diagnosis of blastomycosis.

Laboratory tests such as complement fixation and intradermal skin tests are generally of little value in the diagnosis of blastomycosis.[14,21] A new immunodiffusion test, however, has a greater sensitivity and specificity.[22] Fluorescent antibody preparations have also been developed to permit the rapid and accurate detection of *B. dermatitidis* in clinical material.[23]

When blastomycosis is suspected on clinical grounds, appropriate specimens (sputum, body fluids and tissue) must be obtained and examined microscopically in a sodium hydroxide mount. Fungal cultures are mandatory for confirmation of the disease.

Direct microscopy revealed *B. dermatitidis* in specimens from 90% of the patients. A diagnosis may be made rapidly in this way.

In the yeast form *B. dermatitidis* is a round or oval cell 8 to 10 μm in diameter. It has a thick, refractile cell wall and a broad-based attachment to the daughter cell (Fig. 1); it should not be confused with other

fungi. *Cryptococcus neoformans* has a single bud that pinches off, leaving a markedly attenuated isthmus of attachment to the mother cell and thus assuming a teardrop shape. The interior of *C. neoformans* has a vague and empty appearance, in marked contrast to that of *B. dermatitidis*.[24] *Coccidioides immitis* is characterized by spherules that may be more than 60 μm in diameter and may either be empty or contain endospores, which are round, nonbudding structures 2 to 5 μm in diameter.[24] *Coccidioides* and *Blastomyces* may, on occasion, be confused in a direct mount if the spherule wall of the former is not evident, if there are two endospores that did not separate completely, or if the spherule is immature. *B. brasiliensis* cells vary from 2 to 30 μm in diameter, are spherical to ovate or elliptical and may form chains of three or four cells. The cell wall is thinner in young buds, being only 0.1 to 0.3 μm thick, as compared with 0.5 to 1.0 μm thick in older cells. Buds are attached to the parent cell by a narrow neck; a cell may produce more than one bud at a time.[24] Erythrocytes need not be considered in the differential diagnosis since their biconcavity is so distinctive. Finally, pollen should never be confused with any of these fungi because pollen grains have spiny or striated surfaces, and their walls are of uneven thickness.

Conclusion

The clinical characteristics and epidemiologic features of blastomycosis in our series generally agree with previously published data. However, we have shown that the endemic area in Ontario is much larger than the known focus around Sioux Lookout. The disease may appear in any of the scattered towns across the region north and east of Lake Superior. Even if their practice location seems remote from this region, physicians need only ask patients who present with respiratory complaints "where have you lived or travelled?" to be alerted to the possibility of blastomycosis.

Blastomycosis should be included in the differential diagnosis of pneumonia; often the fungus can be identified promptly through direct microscopy of sputum or other specimens, and its identity is readily confirmed by culture. Although most of the patients in our series survived, a diagnosis made earlier than the average of 15 weeks after presentation might have led to appropriate therapy before the disease had disseminated in the other cases. Blastomycosis is a treatable and curable disease.

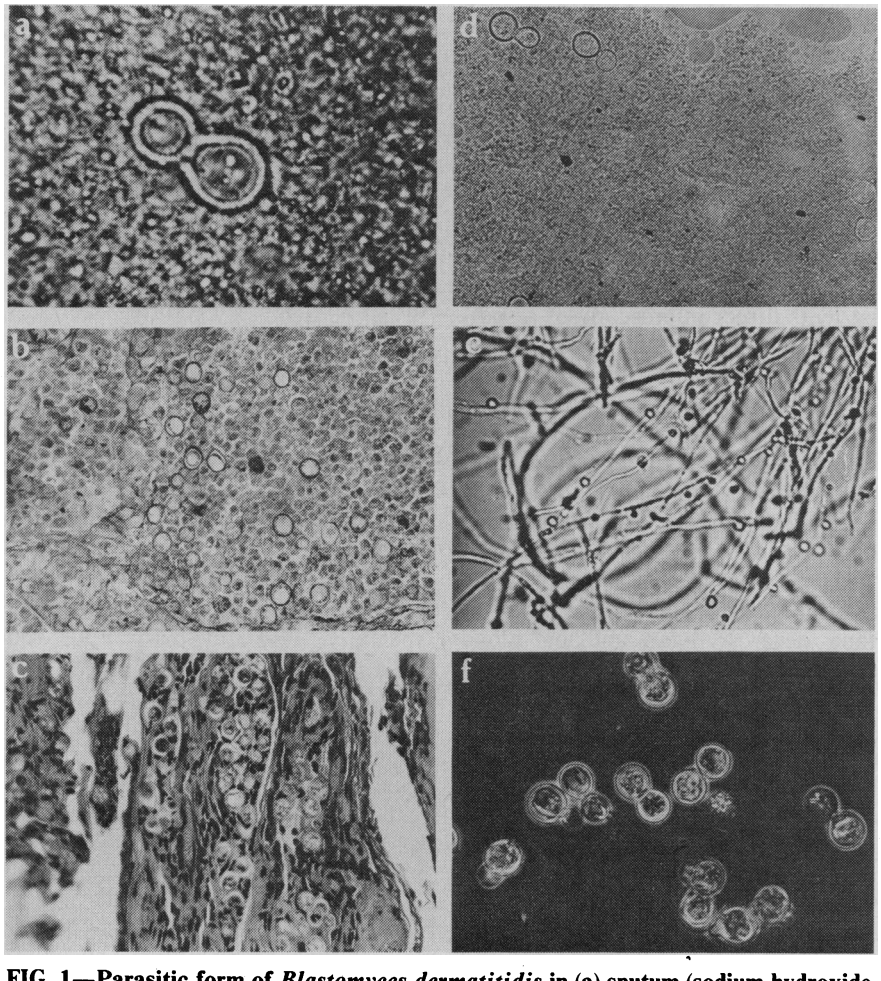

FIG. 1—Parasitic form of *Blastomyces dermatitidis* in (a) sputum (sodium hydroxide [NaOH] preparation, ×1000), (b) lung tissue (periodic acid–Schiff [PAS], ×400), (c) skin biopsy specimen (PAS, ×400) and (d) brain tissue (NaOH, ×400); (e) nonparasitic (saprophytic) form; and (f) organism converted to yeast form at 37°C on a chemically defined medium[6] (×400).

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Adrenal cortical carcinoma: an unusual cause of hyperaldosteronism

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Although secondary hyperaldosteronism due to renal vein thrombosis may occur as a result of renal cell carcinoma or adrenal cortical carcinoma, primary hyperaldosteronism is rarely associated with the latter. This paper describes a patient with adrenal cortical carcinoma who presented with the clinical features of primary hyperaldosteronism 1 year after hypertension had been diagnosed; intravenous pyelography had not been done then. Drug therapy was ineffective, and the patient died 10 weeks after presentation.

Bien que de l'hyperaldostéronisme secondaire à une thrombose d'une veine rénale puisse survenir à la suite d'un cancer des cellules rénales ou d'un cancer du cortex surrénalien, l'hyperaldostéronisme primaire est rarement relié à celui-ci. Cet article décrit le cas d'un patient ayant un cancer du cortex surrénalien vu au moment où il présentait les caractéristiques cliniques d'hyperaldostéronisme primaire, 1 an après qu'on eut diagnostiqué chez lui de l'hypertension. Une pyélographie intraveineuse n'avait pas alors été pratiquée. La chimiothérapie s'avéra inefficace, et le patient mourut 10 semaines après la consultation.

Patients with adrenal cortical carcinoma usually present with symptoms of an enlarging tumour mass and less commonly with clinical evidence of an endocrine abnormality. Of the endocrine abnormalities, Cushing's syndrome, virilization and feminization are the most common.[1] Rarely is an excess of mineralocorticoid a primary manifestation of the tumour. In this article I describe a patient with adrenal cortical carcinoma who presented with clinical features of hyperaldosteronism.

Case report

A 27-year-old man presented to the emergency department of a community hospital complaining of bilateral leg swelling. A year earlier hypertension had been discovered when the patient suffered from headaches and blurred vision. Intravenous pyelography and measurement of the serum electrolyte levels had not been done. Pindolol and triamterene–hydrochlorothiazide, one tablet of each daily, had led to moderate improvement. He voluntarily lost 4.5 kg of body weight. His father had died at age 39 years of a "brain hemorrhage".

The patient was thin, and his blood pressure was 200/120 mm Hg. No hyperpigmentation or cushingoid features were apparent. However, there were retinal exudates and blurring of the optic disc, bilateral leg edema and a palpable mass in the right upper quadrant of the abdomen. Renal bruits were absent.

A chest x-ray film and urinalysis showed no abnormalities. The hemoglobin level was 132 g/l and the leukocyte count 5.5 × 10^9/l. The serum electrolyte levels indicated hypokalemia and metabolic alkalosis (sodium 145 mmol/l, potassium 2.3 mmol/l, chloride 97 mmol/l and bicarbonate 35.2 mmol/l). However, the blood urea nitrogen level, serum creatinine level and creatinine clearance were normal. Intravenous pyelography showed a large right suprarenal mass, and angiography confirmed the presence of a highly vascular tumour.

The hypertension and hypoka-

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